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EXAMINER	
FLOOD, MICHELE C	
ART UNIT	PAPER NUMBER
1655	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/771,711	YOUNG, JEFFREY	
	Examiner	Art Unit	
	MICHELE FLOOD	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 June 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7,8,26-60,65-69 and 74-81* is/are pending in the application.

4a) Of the above claim(s) *7,8 and 26-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *51-60,65-69 and 74-81* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgment is made of the receipt and entry of the amendment filed on June 10, 2009 with the cancellation of Claims 61-64; and the addition of newly added Claims 74-81.

Any rejection set forth in the previous Office action mail dated January 5, 2009 and not repeated herein is withdrawn.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 51-60, 65-69 and 74-81 are under examination.

Response to Arguments

Claim Objections

Claims 78-81 are objected to because of the following informalities:

Each of Claims 78-81 fails to recite an article which agrees with the term "taurine". For instance, each claim recites "an taurine", in line 2. Applicant may overcome the objection by replacing “an” with a to place the claims in proper grammatical order.

There is an apparent misspelling in each of Claims 78-81. Applicant may overcome the objection by replacing “forth” with fourth.

Appropriate correction is required. Newly applied as necessitated by amendment.

Claim Rejections - 35 USC § 112

Claims 51-60, 65-69 and 74-81, as amended, remain/are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Newly applied to Claims 74-81, as necessitated by amendment. The rejection remains for the reason set forth in the previous Office action and for the reason set forth below.

The term "substantially" in Claim 51 is a relative term which renders the claim indefinite. The term "substantially" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Applicant has not traversed the rejection of this claim as set forth in the previous Office action. Therefore, the rejection is maintained.

The metes and bounds of Claims 78-81 are rendered vague and indefinite by the phrase, “said composition further comprises an taurine as a forth active ingredient", because it is unclear as to whether intends to direct the subject matter of the invention to wherein the method composition comprises taurine as a fourth ingredient or another further active ingredient. The lack of clarity renders the claims ambiguous.

All other cited claims depend directly or indirectly from rejected claims and are, therefore, also, rejected under U.S.C. 112, second paragraph for the reasons set forth above.

Claim Rejections - 35 USC § 103

Claim 51, as amended; Claims 53, 54, 57-60, 65 and 67; and newly submitted Claims 74 and 76 remain(s)/are rejected under 35 U.S.C. 103(a) as being unpatentable over Jiang et al. (O or U; Translation of foreign patent document CN 1393264 A provided herein and referred to herein.) and Song et al. (V; Translation of foreign language document provided herein.) in view of Nishimura et al. (R), and further in view of Ebdrup et al. (O), Gorogawa et al. (W) and Hamaoka et al. (X). The rejection stands for the reason set forth in the previous Office action but slightly altered to take into account Applicant's amendment to the claims.

Applicant's arguments have been fully considered but they are not deemed persuasive because the cited references provide the suggestions and motivation to the claimed invention.

Applicant claims a method of treating a living object with non-insulin dependent diabetes, comprising a step of administering to said living object a composition comprising a predetermined amount of berberine as a first active ingredient and a predetermined amount of catalpol as a second active ingredient, in such a manner that when said first and said active ingredients are administered, insulin beta cells of said living object is substantially restored so as to achieve lowering of plasma sugar level. Applicant further claims the method, as recited in claim 51, wherein said composition further comprises an oleanolic acid as a third active ingredient; and, wherein said berberine is extracted from one or more natural herbs selected from the group consisting of Berberis, Chelidonium, Stephniz, Coptis, Phellodendron, and Ziziphus.

Applicant further claims the method, as recited in claim 53, wherein said catalpol is extracted from one or more natural herbs selected from the group consisting of Rehmannia, Verbascum, Paulownia, Globularia, and Adonis. Applicant further claims the method as recited in claim 52, wherein said oleanolic acid is extracted from one or more natural herbs selected from the group consisting of Olea, Swertia, Astrantia, Lonicera, and Beta. Applicant further claims the method as recited in claim 55, wherein said berberine is extracted from one or more natural herbs selected from the group consisting of Berberis, Chelidonium, Stephniz, Coptis, Phellodendron, and Ziziphus, and said catalpol is extracted from one or more natural herbs selected from the group consisting of Rehmannia, Verbascum, Paulownia, Globularia and Adonis. Applicant further claims the method, as recited in claim 51, wherein said composition is prepared into a predetermined form for administration that contains 1 to 300 mg/kg/dl of said berberine. Applicant further claims the method , as recited in claim 53, wherein said composition is prepared into a predetermined form for administration that contains 1 to 300 mg/kg/dl of said berberine; and, wherein said composition is prepared into a predetermined form for administration that contains 5 to 150 mg/kg/dl of said berberine. Applicant further claims the method, as recited in claim 59, wherein said composition is prepared as a draught in water; wherein said composition is prepared as a syrup; wherein said composition is prepared as a cachets; wherein said composition is prepared as a tablet; and, wherein said composition is prepared as a solution. Applicant further claims the method, as recited in claim 51, wherein said composition is prepared into a predetermined form for administration that contains 1 to

300 mg/kg/dl of said active ingredients. Applicant further claims the method, as recited in claim 52, wherein said composition is prepared into a predetermined form for administration that contains 1 to 300 mg/kg/dl of said ingredients. Applicant further claims the method, as recited in claim 54, wherein said composition is prepared into a predetermined form for administration that contains 1 to 300 mg/kg/dl of said ingredients. Applicant further claims the method, as recited in claim 56, wherein said composition is prepared into a predetermined form for administration that contains 1 to 300 mg/kg/dl of said ingredients. Applicant further claims the method, as recited in claim 68, wherein said composition is prepared as a draught in water; wherein said composition is prepared as a syrup; wherein said composition is prepared as a cachets; wherein said composition is prepared as a tablet; and, wherein said composition is prepared as a solution.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Contrary to Applicant's arguments, in no way has the Examiner gleaned any information from Applicant's application to establish a case of obviousness.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the primary references of Jiang and Song were relied upon because they teach the biomechanisms by which berberine exerts its antidiabetic effect when administered in effective amounts to a living subject. For instance, Jiang teaches the oral administration of an effective amount of berberine (0.5g three times a day) extracted from the rhizomes of *Coptis* to humans suffering Type II diabetes to provide a method of treating a living object with non-insulin dependent diabetes and the lowering of plasma sugar level. *See* first paragraph of page 3 and page 10 and 11 of translation, as well as Table 2. Jiang further teaches the berberine ingredient as an insulin receptor sensitizer for the treatment of non-insulin diabetes and demonstrates its enhancement of the expression of peroxisome proliferator-activated receptor (PPAr) gene. Applicant argues that Jiang teaches away from the present invention because Jiang "merely teaches the use of berberine as an additional composition for use with insulin in which the object is to boost up the effect of insulin". However, Applicant's argument is not commensurate in scope to the limitations of the claimed invention because Claim 51, as presently drafted, does not exclude the administration of additional ingredients in the claimed method of

treatment. Furthermore, Jiang expressly teaches that berberine can be used independently or jointly with insulin or other medicines treating Type II diabetes for the treatment of non-insulin dependent diabetes. *See* page 5 of the translated document, lines 5-13, wherein Jiang also teaches, "The inventors discovered through research that berberine can interact with insulin receptor and can significantly enhance the expression of peroxisome proliferator-activated receptor gene (PPARr) gene. Therefore, it can be used as insulin sensitizer for the treatment of Type II diabetes". In another instance, Song teaches orally administering an effective amount of berberine (0.1 g) obtained from Radix *Coptis* to non-insulin dependent diabetic rats fed a high caloric diet to provide a method of treating a living object with non-insulin dependent diabetes and the lowering of plasma sugar level. Song further teaches that berberine inhibited hypersinsulinemia and ameliorated the abnormalities in glucose tolerance and lipid metabolism. The treatment taught by Song also decreased lipid peroxide content and increased superoxide dismutase activity in the liver indicating that berberine has marked antioxidant activity and thus inhibits metabolic disorders resulted from oxidative damage in the non-insulin dependent diabetic. Because the combined teachings of Jiang and Song taught the claimed method of treating a living object with non-insulin dependent diabetes except for administering catalpol as a second active ingredient, the secondary teachings of Nishimura were relied upon because Nishimura taught the extraction of *Rehmannia* to obtain catalpol having antidiabetic effect and aldose reductase inhibitory activity. Thus, at the time the invention was made, one of ordinary skill in the art would have been motivated and would have had a reasonable expectation of success to add

the catalpol taught by Nishimura to the composition used in the method taught by the combined teachings of Jiang and Song to provide the instantly claimed invention because Nishimura taught that catalpol obtained from *Rehmanniae* was useful in the therapy of complications related to diabetes, such as cataract, retinopathy and renopathy. Moreover, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the claim-designated ingredients in the making of the claimed method of treating non-insulin dependent diabetes in a subject in need thereof because it is well known that its *prima facie* obvious to combine two or more ingredients each of which is taught by the prior art to be useful for the same purpose in order to form a third composition which is useful for the same purpose. The idea for combining them flows logically from their having been used individually in the prior art. *In re Pinten,* 459 F. 2d 1053, 173 USPQ 801 (CCPA 1972); *In re Susi,* 58 CCPA 1074, 1079-80; 440 F.2d 442, 445; 169 USPQ 423, 426 (1971); *In re Crockett,* 47 CCPA 1018, 1020-21; 279 F.2d 274, 276-277; 126 USPQ 186, 188 (1960).

Applicant argues:

"The Examiner rejected claims 51-73 (which correspond to claims 51-81 in the present amendment) over Jiang et al. and Song et also in view of Nishimura et al., Ebrup et al. Gorogawa et al., Hamaoka et al and Yoshikawa. Pursuant to 35 U.S.C. 103:

"(a) A patent may not be obtained thought the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the **subject matter as a whole would have been obvious** at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made."

In view of 35 U.S.C. 103(a), it is apparent that to be qualified as a prior art under 35USC103(a), the prior art must be cited under 35USC102(a)~(g) but the disclosure of the prior art and the invention are not identical and there are one or more differences between the subject matter sought to be patented and the prior art. In addition, such differences between the subject matter sought to be patented as a **whole**

and the prior art are obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains.

In other words, the differences between the subject matter sought to be patent as a whole of the instant invention and Jiang which is qualified as prior art of the instant invention under 35USC102(b) are obvious in view of the various cited art at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains.

The applicant respectfully submits that in order to determine whether the differences between the subject matters sought to be patent as a whole of the instant invention and the primary prior arts, Jiang and Song, are obvious in view of the supplemental cited arts, Nishimura et al., Ebrup et al. Gorogawa et al., Hamaoka et al. and Yoshikawa, we have to identify all the differences between the claims of the instant inventions and Jiang and Song. The applicant respectfully identifies the differences between the claims of the instant invention and Jiang and Song as follows.

Referring to the newly amended claim 51, the composition is used for treating living object with non-insulin dependent diabetes mellitus by restoring insulin beta cells, whereas Jiang et al. merely uses Berberine as a supplement and Song merely provides information for the possibility of some therapeutic effect of Berberine. A mere recitation of possible therapeutic effect does not in any way anticipate or suggest any composition for treating living object with non-insulin dependent diabetes mellitus **through restoration of insulin** beta cells. Experiments have shown a promising effect of restoring insulin beta cells by administering berberine and catalpol. This is an **unexpected** result from combining the two active ingredients. The results as demonstrated in Example 13 in relation to the seven indexes, that is: (1) fasting plasma sugar level before and after treatment (FPG), (2) Apolipoprotein AI (APOAI), (3) Apolipoprotein B (APOB), (4) total cholesterol (TC), (5) Triglyceride (TG), (6) High density lipoprotein (HDL), and (7) Low density lipoprotein (LDL) has further support the unexpected results which is only achieved by the subject matter of the present invention. Neither Jiang nor Song and the related cited arts in any way teach, suggest or motivate the use of the two claimed active ingredients for lowering blood glucose level and risk of complications through restoration of insulin beta cells in living objects such as mice.

In the newly amended claim 51, "the composition comprises a berberine as a first active ingredient and a catalpol as a second active ingredient". Jiang et al. merely teaches the use of berberine as an additional composition for use with insulin in which the object is to boost up the-effect of insulin. The use of insulin is contradictory to the rationale of using the composition and is in a way teaches away from the present invention. Song et al. merely provides research data of berberine and is silent on its application or combination effect with other composition. There is no indication of its application or combination effect with Catapol which is the second active ingredient of the present invention. While Jiang et al. teaches away from the present invention, Song et al. is insufficient in having any implication to the present invention, the prima facie case of obviousness is not fully demonstrated by Jiang et al and Song et al. in view of other references.

The applicant further submits that each of the cited references, Jiang et al., Song et al., Nishimura et al., Ebrup et al. Gorogawa et al., Hamaoka et al. and Yoshikawa merely teaches one of the ingredients of the composition as claimed in the instant invention. However, none of the cited references teaches the composition in a whole in combination of all the elements in specific as claimed in claims 51-60, 65-69 and 74-81. The applicant respectfully submits that the cited references fail to anticipate

the distinctive features of the instant invention as claimed. No specific range such as 1 to 300 mg/kg/dl of berberine (as in claims 57, 58, 65-68); dosage of 300mg of berberine and catalpol (as in claims 74, 75); relative ratio of 1:20 to 20:1 by weight of berberine and catalpol (as in claims 76-77) are provided by the references."

Applicant's arguments have been fully considered. However, they are not persuasive for the following reasons. The Office recognizes that the combined references do not specifically teach a method wherein the administering of the ingredients to a living subject provides the claim-functional effect for substantially restoring insulin beta cells of the living subject so as to achieve lowering of plasma sugar level. Therefore, the teachings of Ebdrup, Gorogawa and Hamaoka were relied upon because they substantiate the Examiner's preliminary analysis that it would have been obvious to administer to a living object with non-insulin dependent diabetes a composition comprising a predetermined amount of berberine as a first active ingredient and a predetermined amount of catalpol as a second active ingredient such that when the first and the second active ingredients are administered thereto the subject, insulin beta cells of the living object are substantially restored so as to achieve lowering of plasma sugar level to provide the instantly claimed method of treatment.

Firstly, the teachings of Ebdrup were relied upon because Ebdrup teaches that compounds displaying peroxisome proliferator-activated receptor activation are useful in the treatment of type II diabetes and macrovascular complications associated with type II diabetes and metabolic system disorder by lowering both the overt hypertriglyceridaemia, hyperglycemia, impaired glucose tolerance, insulin tolerance, insulin resistance, obesity, cardiovascular disorders, and apoptosis of insulin beta-cells of islets of Langerhans. Thus, it was known in the art at the time of the invention that

compounds which enhance the expression of the peroxisome proliferator-activated receptor gene, such as the berberine extracted from *Coptis* used in the method taught by Jiang, lower apoptosis of insulin beta-cells of islets of Langerhans and serum blood levels; and thereby are useful in the treatment and complications associated with Type II diabetes.

Secondly, the teachings of Gorogawa were relied upon because Gorogawa teaches, " Oxidative stress is induced under diabetic conditions and causes various forms of tissue damage in patients with diabetes. Recently, pancreatic beta-cells have emerged as a putative target of oxidative stress-induced tissue damage and this seems to explain in part the progressive deterioration of beta-cell function in type 2 diabetes. As a step toward clinical trial of antioxidant for type 2 diabetes, we investigated the possible anti-diabetic effects of probucol, an antioxidant widely used as an anti-hyperlipidemic agent, on preservation of beta-cell function in diabetic C57BL/KsJ-db/db mice. Probucol-containing diet was given to mice from 6 to 16 weeks of age. Immunostaining for oxidative stress markers such as 4-hydroxy-2-nonenal (HNE)-modified proteins and heme oxygenase-1 revealed that probucol treatment decreased reactive oxygen species (ROS) in pancreatic islets of diabetic animals. Oxidative stress is known to enhance apoptosis of beta-cells and to suppress insulin biosynthesis, but probucol treatment led to preservation of beta-cell mass and the insulin content. According to intraperitoneal glucose tolerance tests, the probucol treatment preserved glucose-stimulated insulin secretion and improved glucose tolerance at 10 and 16 weeks: insulin, 280+/-82 vs. 914+/-238 pmol/l (120 min, at 16 weeks; $P<0.05$); glucose,

44.6+/-2.4 vs. 35.2+/-2.6 mmol/l (120 min, at 16 weeks; P<0.05). Thus, our present observations demonstrate the potential usefulness of probucol for treatment of type 2 diabetes." Thus, it was known in the art at the time of the invention that antioxidants having anti-lipidemic effect and glucose tolerance inhibiting effect, such as the berberine extracted from Coptis used in the method taught by Song, preserve insulin beta-cell content and lower serum blood levels; and thereby suggest the use of antioxidant therapy for the treatment of non-insulin dependent diabetes.

Thirdly, the teachings of Hamaoka were relied upon because Hamaoka teaches that overexpression of aldose reductase in pancreatic beta-cells induced by superoxide dismutase promotes apoptosis and suggests the use of aldose reductase inhibitors for the treatment and pathogeneses of diabetic complications. Thus, it was suggested in the art at the time the invention was made that aldose reductase inhibitors, such as the catalpol extracted from *Rehmanniae* and having beneficial effects in ameliorating diabetic complications taught by Nishimura and exerting inhibitory activity against aldose reductase, lower apoptosis of insulin beta-cells of islets; and thereby is useful in the treatment and complications associated with Type II diabetes.

Given the teachings of the references as a whole, an artisan of ordinary skill would have had a reasonable expectation that combining the berberine, as used in the method taught by the combined teachings of Jiang and Song, with the catalpol taught by Nishimura would be successful in providing a method of treating non-insulin dependent diabetes comprising a step of administering to said living object a composition comprising a predetermined amount of berberine as a first active ingredient

and a predetermined amount of catalpol as a second active ingredient, in such a manner that when said first and said active ingredients are administered, insulin beta cells of said living object is substantially restored so as to achieve lowering of plasma sugar level. This reasonable expectation of success would have motivated the artisan to use the ingredients taught by the combined teachings of Jiang, Song and Nishimura to arrive at the instantly claimed invention, given the beneficial functional effects for each of berberine and catalpol that they have shown in the treatment of Type II diabetes.

The combined references do not specifically teach using the composition in the amounts or ratio ranges claimed by Applicant. The amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). However, the references teach that the amounts of berberine and catalpol can be varied. Thus, the combined teachings of Jiang, Song and Nishimura recognize that the amount of the claim-designated ingredients can be modified. Therefore, it would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient to add in order to best achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, this optimization of ingredient amount would have been obvious at the time of Applicant's invention.

The combined references do not specifically teach using the composition in the dose range amounts claimed by Applicant. The amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Therefore, it would have been customary for an artisan of ordinary skill to determine the optimal amount of the ingredient to administer in order to best achieve the desired results. For instance, the amount of a specific ingredient in a composition and the dosage frequency for treating a patient with a drug is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize, given that such determination is generally based on the severity of the disease, the age, weight and/or the sex of the patient, and the efficacy of the drug treatment. Moreover, the adjustment of particular conventional working conditions (*e.g.,* determining a result-effective means of administering said first active ingredient at a dosage of 300 mg and said second active ingredient at a dosage of 300 mg into a subject, for three times a day) is deemed merely a matter of judicious selection and routine optimization which would have been well within the purview of either one of ordinary skill in the art or the skilled artisan at the time the invention was made. Thus, absent some demonstration of unexpected results from the claimed parameters, this optimization of ingredient amount for administration to provide a method of growth promotion in an animal in need thereof would have been obvious at the time of Applicant's invention.

With regard to the claim limitations of Claim 60, wherein Applicant directs the instantly claimed method to a composition prepared as either a draught in water, a syrup, a cachet and a solution, it also would have been *prima facie* obvious to one of ordinary skill in the art practicing the invention to modify the form of the composition taught by the combined references by preparing the composition as either a draught in water, a syrup, a cachet or a solution to provide the instantly claimed method because at the time the invention was made each of the claim-designated pharmaceutical forms were known to be conventional and useful vehicles for the delivery of an anti-diabetic agent for the treatment of non-insulin diabetes mellitus. Therefore, one of ordinary skill in the art would have been motivated and had a reasonable expectation that such a modification of the teachings would be successful.

Thus, with Jiang and Song teaching the biomechanism by which berberine exerts its antidiabetic effect for lowering of plasma sugar level in the treatment of subjects with non-insulin dependent diabetes is enhancement of peroxisome proliferator-activated receptor (PPAr) gene and/or anti-oxidant activity; and, with Nishimura teaching the biomechanism which catalpol exerts its antidiabetic effect for lowering of plasma sugar level in the treatment of subjects with non-insulin dependent diabetes is inhibition of aldose reductase activity; and, with each of Ebdrup, Gorogawa and Hamaoka providing the motivation and suggestion to use compositions displaying peroxisome proliferator-activated receptor activation or antioxidant activity or aldose reductase inhibitory activity, respectively, to restore or preserve beta-cell function and/or insulin beta-cell content in the treatment of subjects with Type II diabetes, it would have been obvious to

one of ordinary skill in the art at the time the invention was made to administer to a living object in need of treatment of Type II diabetes a composition comprising an effective amount of a composition comprising a predetermined amount of berberine as a first active ingredient and a predetermined amount of catalpol as a second active ingredient, in such a manner that when the first and second active ingredients are administered insulin beta cells of the living object is substantially restored so as to achieve lowering of plasma sugar level as suggested by the cited references.

As each of the references clearly indicate that the various proportions and amounts of the ingredients used in the claimed composition or the claimed composition/pharmaceutical combinations are result variables, they would have been routinely optimized by one of ordinary skill in the art in practicing the invention disclosed by that reference.

Therefore, the invention as a whole was clearly *prima facie* obvious in the absence to the contrary.

Claim 51, as amended; Claims 52-56, 66 and 68, 69; and newly submitted Claims 74-77 remain(s)/ are rejected under 35 U.S.C. 103(a) as being unpatentable over Jiang et al. (O or U; Translation of foreign patent document CN 1393264 A provided herein and referred to herein.) and Song et al. (V; Translation of foreign language document provided herein.) and Nishimura et al. (R) in view of Yoshikawa et al. (U1), and further in view of Ebdrup et al. (O), Gorogawa et al. (W) and Hamaoka et al. (X). The rejection stands for the reason set forth in the previous Office action but

slightly altered to take into account Applicant's amendment to the claims; and, for all of the reasons set forth immediately above.

Applicant further claims the method, as recited in claim 51, wherein the composition further comprise an oleanolic acid as third active ingredient.

Applicant's arguments have been fully considered but they are not deemed persuasive because the cited references provide the suggestions and motivation to the claimed invention.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the combined

teachings of Jiang, Song and Nishimura made obvious over the teachings of Ebdrup, Gorogawa and Hamaoka were relied upon for the reason set forth in the previous Office action and for all of the reason set forth immediately above. Because the combined references taught the instantly claimed invention except for oleanolic acid, the secondary reference of Yoshikawa was relied upon because Yoshikawa taught an oleanolic acid obtained from *Beta vulgaris* exhibiting hypoglycemic activity in oral glucose tolerance test in rats. Moreover, it would have been obvious to one of ordinary skill in the art at the time the invention was made to add the claim-designated ingredient in the making of the claimed method of treating non-insulin dependent diabetes in a subject in need thereof because it is well known that its *prima facie* obvious to combine two or more ingredients each of which is taught by the prior art to be useful for the same purpose in order to form a third composition which is useful for the same purpose. The idea for combining them flows logically from their having been used individually in the prior art. *In re Pinten,* 459 F. 2d 1053, 173 USPQ 801 (CCPA 1972); *In re Susi,* 58 CCPA 1074, 1079-80; 440 F.2d 442, 445; 169 USPQ 423, 426 (1971); *In re Crockett,* 47 CCPA 1018, 1020-21; 279 F.2d 274, 276-277; 126 USPQ 186, 188 (1960).

The references do not specifically teach using the composition in the amounts or ratio ranges claimed by Applicant. The amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

However, the references teach that the amounts of berberine, catalpol and oleanolic acid can be varied. Thus, the combined teachings of Jiang, Song, Nishimura and Yoshikawa recognize that the amount of the claim-designated ingredients can be modified. Therefore, it would have been customary for an artisan of ordinary skill to determine the optimal amount of the ingredient to add in order to best achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, this optimization of ingredient amount would have been obvious at the time of Applicant's invention.

The combined references do not specifically teach using the composition in the dose range amounts claimed by Applicant. The amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Therefore, it would have been customary for an artisan of ordinary skill to determine the optimal amount of the ingredient to administer in order to best achieve the desired results. For instance, the amount of a specific ingredient in a composition and the dosage frequency for treating a patient with a drug is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize, given that such determination is generally based on the severity of the disease, the age, weight and/or the sex of the patient, and the efficacy of the drug treatment. Moreover, the adjustment of particular conventional working conditions (*e.g.,* determining a result-

effective means of administering said first active ingredient at a dosage of 300 mg and aid second active ingredient at a dosage of 300 mg into a subject, for three times a day) is deemed merely a matter of judicious selection and routine optimization which would have been well within the purview of either one of ordinary skill in the art or the skilled artisan at the time the invention was made. Thus, absent some demonstration of unexpected results from the claimed parameters, this optimization of ingredient amount for administration to provide a method of growth promotion in an animal in need thereof would have been obvious at the time of Applicant's invention.

With regard to the claim limitations of Claim 69 wherein Applicant directs the instantly claimed method to a composition prepared as either a draught in water, a syrup, a cachet and a solution, it also would have been *prima facie* obvious to one of ordinary skill in the art practicing the invention to modify the form of the composition taught by the combined references by preparing the composition as either a draught in water, a syrup, a cachet or a solution to provide the instantly claimed method because at the time the invention was made each of the claim-designated pharmaceutical forms were known to be conventional and useful vehicles for the delivery of an anti-diabetic agent for the treatment of non-insulin diabetes mellitus. Therefore, one of ordinary skill in the art would have been motivated and had a reasonable expectation that such a modification of the teachings would be successful.

As the references indicate that the various proportions and amounts of the ingredients used in the claimed method are result effect variables, they would have

been routinely optimized by one of ordinary skill in the art in practicing the invention disclosed by the references.

Accordingly, the claimed invention was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, especially in the absence of evidence to the contrary.

Claims 51, 53, 54, 57-60, 65, 67, 74 and 76, as amended, are rejected under 35 U.S.C. 103(a) as being unpatentable over Song et al. (V; Translation of foreign language document provided herein.), Lee (V) and Nishimura et al. (R) in view of Gorogawa et al. (W) and Hamaoka et al. (X). Newly applied as necessitated by amendment.

Song beneficially teaches orally administering an effective amount of berberine (0.1 g) obtained from Radix *Coptis* to non-insulin dependent diabetic rats fed a high caloric diet to provide a method of treating a living object with non-insulin dependent diabetes and the lowering of plasma sugar level. Song further teaches that berberine inhibited hypersinsulinemia and ameliorated the abnormalities in glucose tolerance and lipid metabolism. The treatment taught by Song also decreased lipid peroxide content and increased superoxide dismutase activity in the liver indicating that berberine has marked antioxidant activity and thus inhibits metabolic disorders resulted from oxidative damage in the non-insulin dependent diabetic. In another instance, Lee beneficially demonstrates the aldose reductase inhibitory activity of berberine isolated from *Coptis*.

Lee further suggests use of berberine aldose reductase inhibitors from *Coptis* as natural plant sources for the treatment of diabetes mellitus.

Nishimura beneficially teaches the extraction of *Rehmannia* to obtain catalpol having antidiabetic effect and aldose reductase inhibitory activity.

The combined teachings of Song, Lee and Nishimura, as set forth above, teach a method of treating a living object with non-insulin dependent diabetes comprising administering a composition comprising an effective amount of berberine and an effective amount of catalpol to a subject in need thereof to achieve lowering of plasma sugar level. The combined references do not specifically teach a method of treating a living object with non-insulin independent diabetes wherein when the ingredients administered to a living subject, insulin beta cells of the living subject are substantially restored so as to achieve lowering of plasma sugar level.

Firstly, Gorogawa teaches, " Oxidative stress is induced under diabetic conditions and causes various forms of tissue damage in patients with diabetes. Recently, pancreatic beta-cells have emerged as a putative target of oxidative stress-induced tissue damage and this seems to explain in part the progressive deterioration of beta-cell function in type 2 diabetes. As a step toward clinical trial of antioxidant for type 2 diabetes, we investigated the possible anti-diabetic effects of probucol, an antioxidant widely used as an anti-hyperlipidemic agent, on preservation of beta-cell function in diabetic C57BL/KsJ-db/db mice. Probucol-containing diet was given to mice from 6 to 16 weeks of age. Immunostaining for oxidative stress markers such as 4-hydroxy-2-nonenal (HNE)-modified proteins and heme oxygenase-1 revealed that probucol

treatment decreased reactive oxygen species (ROS) in pancreatic islets of diabetic animals. Oxidative stress is known to enhance apoptosis of beta-cells and to suppress insulin biosynthesis, but probucol treatment led to preservation of beta-cell mass and the insulin content. According to intraperitoneal glucose tolerance tests, the probucol treatment preserved glucose-stimulated insulin secretion and improved glucose tolerance at 10 and 16 weeks: insulin, 280+/-82 vs. 914+/-238 pmol/l (120 min, at 16 weeks; $P<0.05$); glucose, 44.6+/-2.4 vs. 35.2+/-2.6 mmol/l (120 min, at 16 weeks; $P<0.05$). Thus, our present observations demonstrate the potential usefulness of probucol for treatment of type 2 diabetes." Thus, it was known in the art at the time of the invention that antioxidants having anti-lipidemic effect and glucose tolerance inhibiting effect, such as the berberine extracted from *Coptis* used in the method taught by Song, preserve insulin beta-cell content and lower serum blood levels; and thereby suggest the use of antioxidant therapy for the treatment of non-insulin dependent diabetes.

Secondly, Hamaoka teaches that overexpression of aldose reductase in pancreatic beta-cells induced by superoxide dismutase promotes apoptosis and suggests the use of aldose reductase inhibitors for the treatment and pathogeneses of diabetic complications. Thus, it was suggested in the art at the time the invention was made that aldose reductase inhibitors, such as the berberine extracted from *Coptis* and having blood sugar lowering effect as taught by Song and having aldose reductase inhibitory activity as taught by Lee; and, such as the catalpol extracted from *Rehmanniae* and having beneficial effects in ameliorating diabetic complications as

taught by Nishimura, lower apoptosis of insulin beta-cells of islets; and thereby are useful in the treatment and complications associated with Type II diabetes.

Therefore, with Song and Lee teaching the biomechanism by which berberine exerts its antidiabetic effect for lowering of plasma sugar level in the treatment of subjects with non-insulin dependent diabetes is enhancement of anti-oxidant activity and/or aldose reductase inhibitory activity; and, with Nishimura teaching the biomechanism by which catalpol exerts its antidiabetic effect for lowering of plasma sugar level in the treatment of subjects with non-insulin dependent diabetes is inhibition of aldose reductase activity; and, with each of Gorogawa and Hamaoka providing the motivation and suggestion to use compositions displaying antioxidant activity or aldose reductase inhibitory activity, respectively, to restore or preserve beta-cell function and/or insulin beta-cell content in the treatment of subjects with Type II diabetes, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer to a living object in need of treatment of Type II diabetes a composition comprising an effective amount of a composition comprising a predetermined amount of berberine as a first active ingredient and a predetermined amount of catalpol as a second active ingredient, in such a manner that when the first and second active ingredients are administered insulin beta cells of the living object is substantially restored so as to achieve lowering of plasma sugar level as suggested by the cited references.

The references do not specifically teach using the composition in the amounts or weight ratios claimed by Applicant. The amount of a specific ingredient in a composition

is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). However, the references teach that the amounts of berberine and catalpol can be varied. Thus, the combined teachings of Song, Lee and Nishimura recognize that the amount of the claim-designated ingredients can be modified. Therefore, it would have been customary for an artisan of ordinary skill to determine the optimal amount of the ingredient to add in order to best achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, this optimization of ingredient amount would have been obvious at the time of Applicant's invention.

The combined references do not specifically teach using the composition in the dose range amounts claimed by Applicant. The amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Therefore, it would have been customary for an artisan of ordinary skill to determine the optimal amount of the ingredient to administer in order to best achieve the desired results. For instance, the amount of a specific ingredient in a composition and the dosage frequency for treating a patient with a drug is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize, given that

such determination is generally based on the severity of the disease, the age, weight and/or the sex of the patient, and the efficacy of the drug treatment. Moreover, the adjustment of particular conventional working conditions (*e.g.,* determining a result-effective means of administering said first active ingredient at a dosage of 300 mg and said second active ingredient at a dosage of 300 mg into a subject, for three times a day) is deemed merely a matter of judicious selection and routine optimization which would have been well within the purview of either one of ordinary skill in the art or the skilled artisan at the time the invention was made. Thus, absent some demonstration of unexpected results from the claimed parameters, this optimization of ingredient amount for administration to provide a method of growth promotion in an animal in need thereof would have been obvious at the time of Applicant's invention.

With regard to the claim limitations of Claim 60 wherein Applicant directs the instantly claimed method to a composition prepared as either a draught in water, a syrup, a cachet and a solution, it also would have been *prima facie* obvious to one of ordinary skill in the art practicing the invention to modify the form of the composition taught by the combined references by preparing the composition as either a draught in water, a syrup, a cachet or a solution to provide the instantly claimed method because at the time the invention was made each of the claim-designated pharmaceutical forms were known to be conventional and useful vehicles for the delivery of an anti-diabetic agent for the treatment of non-insulin diabetes mellitus. Therefore, one of ordinary skill in the art would have been motivated and had a reasonable expectation that such a modification of the teachings would be successful.

As the references indicate that the various proportions and amounts of the ingredients used in the claimed method are result effect variables, they would have been routinely optimized by one of ordinary skill in the art in practicing the invention disclosed by the references.

Accordingly, the claimed invention was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, especially in the absence of evidence to the contrary.

Claims 51-60, 65-69 and 74-81, as amended, are rejected under 35 U.S.C. 103(a) as being unpatentable over Song et al. (V; Translation of foreign language document provided herein.), Lee (V1) and Nishimura et al. (R) in view of Yoshikawa et al. (U1), Chang (W1) and Zhang (S), and further in view of Gorogawa et al. (W) and Hamaoka et al. (X). Newly applied as necessitated by amendment.

Applicant further claims a method as recited in either claim 54, 60, 68 or 75, the composition further comprises a taurine as a forth active ingredient.

The combined teachings of Song, Lee, Nishimura, Gorogawa and Hamaoka are set forth above. The combined references teach the claimed invention except for oleanolic acid and taurine. However, addition of the claim-designated ingredients to the method taught by the combined references to provide the claimed method would have been obvious to the artisan of ordinary skill because at the time of the invention Yoshikawa taught an oleanolic acid obtained from *Beta vulgaris* exhibiting hypoglycemic

activity in oral glucose tolerance test in rats; Chang taught a method of administering an effective amount of a composition comprising taurine to diabetic subjects for the protection and preservation of pancreatic beta-cells and suggests taurine supplementation for prevention and treatment of non-insulin dependent diabetes; and Zhang taught a composition comprising oleanolic acid and taurine that was useful in treating type II diabetes having no toxic-effect as well as positive preventing effect on complications of diabetes. Moreover, it would have been obvious to one of ordinary skill in the art at the time the invention was made to add the claim-designated ingredients in the making of the claimed method of treating non-insulin dependent diabetes in a subject in need thereof because it is well known that its *prima facie* obvious to combine two or more ingredients each of which is taught by the prior art to be useful for the same purpose in order to form a third composition which is useful for the same purpose. The idea for combining them flows logically from their having been used individually in the prior art. *In re Pinten,* 459 F. 2d 1053, 173 USPQ 801 (CCPA 1972); *In re Susi,* 58 CCPA 1074, 1079-80; 440 F.2d 442, 445; 169 USPQ 423, 426 (1971); *In re Crockett,* 47 CCPA 1018, 1020-21; 279 F.2d 274, 276-277; 126 USPQ 186, 188 (1960).

The references do not specifically teach using the composition in the amounts or weight ratios claimed by Applicant. The amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

However, the references teach that the amounts of berberine and catalpol can be varied. Thus, the combined teachings of Song, Lee and Nishimura recognize that the amount of the claim-designated ingredients can be modified. Therefore, it would have been customary for an artisan of ordinary skill to determine the optimal amount of the ingredient to add in order to best achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, this optimization of ingredient amount would have been obvious at the time of Applicant's invention.

The combined references do not specifically teach using the composition in the dose range amounts claimed by Applicant. The amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Therefore, it would have been customary for an artisan of ordinary skill to determine the optimal amount of the ingredient to administer in order to best achieve the desired results. For instance, the amount of a specific ingredient in a composition and the dosage frequency for treating a patient with a drug is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize, given that such determination is generally based on the severity of the disease, the age, weight and/or the sex of the patient, and the efficacy of the drug treatment. Moreover, the adjustment of particular conventional working conditions (*e.g.,* determining a result-effective means of administering said first active ingredient at a dosage of 300 mg and

said second active ingredient at a dosage of 300 mg into a subject, for three times a day) is deemed merely a matter of judicious selection and routine optimization which would have been well within the purview of either one of ordinary skill in the art or the skilled artisan at the time the invention was made. Thus, absent some demonstration of unexpected results from the claimed parameters, this optimization of ingredient amount for administration to provide a method of growth promotion in an animal in need thereof would have been obvious at the time of Applicant's invention.

With regard to the claim limitations of Claims 60 and 69 wherein Applicant directs the instantly claimed method to a composition prepared as either a draught in water, a syrup, a cachet and a solution, it also would have been *prima facie* obvious to one of ordinary skill in the art practicing the invention to modify the form of the composition taught by the combined references by preparing the composition as either a draught in water, a syrup, a cachet or a solution to provide the instantly claimed method because at the time the invention was made each of the claim-designated pharmaceutical forms were known to be conventional and useful vehicles for the delivery of an anti-diabetic agent for the treatment of non-insulin diabetes mellitus. Therefore, one of ordinary skill in the art would have been motivated and had a reasonable expectation that such a modification of the teachings would be successful.

As the references indicate that the various proportions and amounts of the ingredients used in the claimed method are result effect variables, they would have been routinely optimized by one of ordinary skill in the art in practicing the invention disclosed by the references.

Accordingly, the claimed invention was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, especially in the absence of evidence to the contrary.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MICHELE FLOOD whose telephone number is (571)272-0964. The examiner can normally be reached on 7:00 am - 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Terry McKelvey can be reached on 571-272-0775. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Michele Flood
Primary Examiner
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MCF
October 26, 2009

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